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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/922,066	08/03/2001	Thierry Godel	20706	8721

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EXAMINER
PATEL, SUDHAKER B

ART UNIT	PAPER NUMBER
1624	12

DATE MAILED: 06/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/922,066	T. Godel et al
Examiner	**Art Unit**
SUDHAKER PATEL,D.Sc.Tech.	1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 29, 2003*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-69* is/are pending in the application.

4a) Of the above, claim(s) *10-12, 16-34, 36-38, 46-49, and 52-67* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-9, 13-15, 35, 39-45, 50, 51, 68, and 69* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☒ Interview Summary (PTO-413) Paper No(s). *11*
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

I. ***Election/Restriction***

Applicant's election with traverse of species in Paper No. 9 dated 4/29/03 is acknowledged. The traversal is on the ground(s) that the Office has not shown any serious burden for including other definitions of R,R2, R3, R3',X, R4 and R4'. This is not found persuasive because:

1. Examiner found prior art(s) and reference(s) which claim similar subject matter as claimed herein.
2. Additionally, variables when considered simultaneously with other components e.g. R1 and X will provide multiples of species which are difficult to examine thoroughly on individual basis within the time at disposal to examiner for a patent.
3. Although, the main core is 4-phenyl-pyridine, variables R1 and X will give either same or different main class(es), but multiples of subclasses as per the U. S. Patent classification system as outlined bellow.

The core for this application is 4-phenyl pyridine(which falls in) class 546, when the R1 component is piperazine, the main class is 544 which supersedes class 546, and the search for class 546 is not equivalent to search for class 544.

4. When the core is 1,4 oxazinone as recited in Example 11 and claim 52, the class is 544, but subclass(es) are different(subclass 106) than 1,4-diazine e.g. piperazine will fall in subclass 358.
5. The number of hits generated for some of the other structures are as follows:

Example 15 wherein R1 is pyrrole or its derivatives will generate:	863;
Example 5 wherein R1 is pyridine or its partially hydrogenated form:	410;
Example 40 wherein R1 is 1,2 oxazole:	356;
Example 62 wherein R1 is 1,2,4 oxadiazole:	225;
Example 93 wherein R1 is 1,2 thiazole:	590;
Example 101 wherein R1 is 1,24 triazole:	479.

The components R/R2; R4/R4' can also form fusion, and the bicyclic rings formed are not chemical equivalent to phenyl rings.

Additionally, the bridges as represented by components X, will generated multiples of different compounds which are different from each other.

Therefore, for each main class, the utility class will add more search. It is this combined thorough additional search which is time consuming, and therefore burdensome to examiner.

6. Examiner searched the species of Example 1 of claim 8 as per the guidelines provided in MPEP 803.02, which are followed for examination.

The species of Example 1 has following meanings for variables:

R1 = 6-membered non-aromatic heterocycle(1,4-diazine/piperazine) consisting of 2 N as heteroatoms and end N is (un)substituted by -C(O)(R') wherein R' is lower alkyl which is substituted by C(O) R'‘' wherein R'‘' is H i.e. piperazine N is having a bridge = -CO-CH2-OH;

(R)n = H;

m = zero;

R2 = alkyl or halogen;

X = -CO-N(R8)-;

R3/R3' = H;

R4/R4' = CF3, and R4, R4" are in 3,5-position compared to -X-CH2- bridge;

R/R2 or R4/R4' = open & not forming a fusion with the ring.

As no prior art was not found, the search was expanded to R1 = R1' =R5 = H. Additional search revealed prior art(s) See new rejections bellow. As per the guide lines stated above, the search is limited to various variables having values as stated above. All other meanings of R1, R, R2, X, R3/R3',R/R2 or R4/R4' than stated above are held withdrawn from further consideration.

Therefore, claims 10-12,16-18,19-20,21-34,36-38,46,47,48,49,52-67 are withdrawn from further consideration.

Since claims 1-9,13-15,35,39-45,50-51,68-69 link with other inventions, this application will be examined bearing in mind the subject matter of species of Example 1 only.

The restriction requirement is still deemed proper for the reasons stated in earlier Office communication paper # 8 dated 1/29/03 and also for the additional reasons stated earlier, and is therefore maintained.

II. Rejections withdrawn:

1. Applicants' Declaration under 37 CFR 1.132 dated 4/29/03 is acknowledged. Based on this declaration the rejections made under 35 U.S.C. 102(e) has been withdrawn. .

2. Applicants arguments and remarks are sufficient to overcome the rejections made under 35 U.S.C.112 para second.

Upon further review and reconsideration, it is found that this application is not ready for allowance at this stage for following rejections(see interview summary dated 5/23/2003).

III. New Rejections:

IIIA. ***Priority***

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119 (a)-(d). The certified copy has been filed in this Application No. 09922066 , which was filed on 8/3/2001.

The claim for foreign priority date 8/8/200 ***can not*** be granted for the instant U.S.Application Sr. No. 09922066 filed 8/3/2001, because the instant claims do not recite the same subject matter as claimed in the EPO 00117003 filed 8/8/2000.

R1 and R2 variables of instant claim 1 are recited in a different way than the EPO application. This will raise additional issues under 35 U.S.C. 112 para one and second.

IIIB. ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-9,13-15,35,39-45,50-51,69 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No.6297375. Although the conflicting claims are not identical, they are not

patentably distinct from each other because ref.'375 claim 1 encompasses the subject matter claimed herein in the following manner:

(R1)p

R4
X
/(CH2)-
R3/R3'
R2/R2'

R1/R

=Instant (R)n= Halogen/H; R
=R2 = lower alkyl/ alkoxy/ halogen/CF3;
=R1 =H;
= X =CONR8/ -NR8CO-O/(CH2)pNR8;
=R3/R3'= alone or with fusion;
=R4/R4'=H/halogen/CF3/alkoxy & fusion;
=R2/R forming fusion.

Thus, it would have been obvious to one skilled in the art at the time the invention was made to be motivated to make instant compound(s) e.g.. with. R1 other than H and also expect the compounds so obtained to have biological properties and find out the instantly proposed utility. It has been held that a prior art disclosed genus of useful compounds is sufficient to render prima facie obvious a species falling within a genus. See In re Susi, 440 F.2d, 442, 169 USPQ 423, 425 (CCPA 1971), followed by the Federal Circuit in Merck & Co. V. Biocraft Laboratories, 847 F.2d 804, 10 USPQ 2d 1843, 1846 (Fed. Cir. 1989).

IV. *Claim Rejections - 35 U.S.C. § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1,3-9,13-15,35,39-45,50-51,69 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S.P. 4745123 also cited as Chemical Abstract DN 108:186578.Instant compounds read onto the ref. '123 in following way:

Reference U.S.P. 4745123:

R4(see col.3 lines 7-21 & 52-54) = Phenyl/substituted phenyl with halogen,alkyl,alkoxy;

R3=COR'R" & R'=H/alkyl;R"= substituted phenylalkyl =X = COCH2- substituted phenyl;

H =R1 = -(CR' R")m-R5 = H with m zero.

See also compounds 7 of the reaction scheme in column 6 lines 34-40, and also compound 46 in Table D columns 13/14 wherein R3 = CONHCH2-Phenyl, and compounds #33,34, 19 which show mono and di substitutions on to phenyl ring.

Additionally the compound represented by CAS RN # 114120-64-8 (= 3-pyridine carboxamide, 4-phenyl-N-(phenyl methyl) is encompassed by instant claim 1.

V. *Claim Rejections - 35 U.S.C. § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 68 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of headache, does not reasonably provide enablement for the treatment of all other diseases encompassed by the instant claims. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with this claim.

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1). The nature of the invention, 2). the state of the prior art, 3). the predictability or lack thereof in the art, 4). the amount of direction or guidance present, 5). the presence or absence of working examples, 6). the breadth of the claims, and 7). the quantity of experimentation needed.

1) The nature of the invention: The method of use claim is drawn in part to alleviating the symptoms of patient having a disease state treatable by modulation of NK-1 receptor antagonists. The specification(pages 1-2, and 5) discloses that these diseases include inflammation, HIV infections, morphine withdrawal symptoms,, Alzheimer's disease, cardiovascular changes, multiple sclerosis, oedema, CNS disorders and others, and there is no enablement for the of all these diseases..

2) The state of the prior art: There are no known compounds of similar structure which have been demonstrated to treat Alzheimer's disease nor is there any compound that can be used to treat drug addiction, drug and alcohol withdrawal symptoms by a single compound. For example, the notion that a compound could be effective against chemical substance abuse or withdrawal caused by the cessation of intake of chemical substances in general is absolutely contrary to our current

understanding of how chemical dependencies operate. There is not, and probably never will be, a pharmacological treatment for "chemical substance abuse or withdrawal caused by the cessation of intake of chemical substances" generally. That is because "chemical substance/drug abuse or withdrawal caused by the cessation of intake of chemical substances" is not a single disease or cluster of related disorders, but in fact, a collection with relatively little in common. Addiction to barbiturates, alcohol, cocaine, opiates, amphetamines, benzodiazepines, nicotine, etc. all involve different parts of the CNS system; different receptors in the body. For example, cocaine binds at the dopamine reuptake transmitter. Heroin addiction, for example, arises from binding at the opiate receptors, cigarette addiction from some interaction at the nicotinic acid receptors, many tranquilizers involve the benzodiazepine receptor, alcohol involves yet another system, etc. All attempts to find an pharmaceutical to treat chemical addictions generally have thus failed. Alzheimer's disease is treated, albeit not successfully, using acetylcholine esterase inhibitors and Parkinson's disease using dopamine receptors. A disease in the central or peripheral system is not a single disease but embraces disease that are not related or even "opposites"; headache, arthritis and asthma are covered and diseases that are not treatable pharmacologically are also embraced (e.g. Parkinson's disease, Crohn's disease, psychosis).

3) The predictability or lack th reof in the art: It is presumed in the treatment of the diseases claimed herein there is a way of identifying any and all of the diseases which

are responsive to the activity of nicotinic ACh receptor modulators. There is no evidence of record which would enable the skilled artisan in the identification of the diseases treatable with the disorders claimed herein.

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses present for treatment of the disorders recited.

6) The breadth of the claims: The claims are drawn to disorders that are not related and whose treatment is unknown.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Following reference is cited to show the state of art related to Alzheimer's disease:

Coyle et al(Science Vol.219, pages 1184-1190(1983)) cites in the summary that:" These cholinergic neurons provide widespread innervation of the cerebral cortex and related structures and appear to play an important role in cognitive functions, especially memory". The authors conclude (see page 1189) that:" The identification of a transmitter-specific pathway selectively affected in a major form of dementia is an important step in the design of diagnostic studies, investigations of pathogenic mechanisms, and the development of therapeutic approaches to these debilitating neuropsychiatric disorders".

Specification remains silent about various assays and test methods for compounds of Formula (I) which are expected to exhibit NK-1, substance P antagonistic activity.

Claim 68 as recited includes: " Disease state treatable by modulation of NK-1 receptor antagonists".

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claim.

Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a single compound for a method of alleviating the symptoms of any and all diseases. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has been achieved, In re Ferens, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, Genentech vs. Novo Nordisk, 42 USPQ 2nd 1001, 1006.All available drug for treating Alzheimer's disease or Parkinsons' disease could be used in a limited way, and provide protection mostly with side effects.

VII. ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker Patel, D.Sc. Tech., whose telephone number is (703) 308 4709. The examiner can normally be reached on Monday thru' Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by the phone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah can be reached at (703) 308 4716 or Sr. Examiner Mr. Richard Raymond at (703)308 4523.A facsimile center has been established for Group 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or (703) 305-3592.Any inquiry of general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 1235.

Mukund J. Shah

Mukund Shah

Supervisory Patent Examiner

Art Unit 1624

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May 18, 2003